Mapping ALSFRS-R and ALSUI to EQ-5D in patients with motor neurone disease

Moore, Alan; Young, Carolyn A.; Hughes, Dyfrig

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Highlights

1. What is already known about this topic?

The Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R) is the preferred measure of health outcome in clinical trials of interventions in motor neurone disease.

Preference-based measures are rarely used within the field of motor neurone disease.

2. What does the paper add to existing knowledge?

The mapping provides an algorithm to link a validated and commonly used measure of health outcome in motor neurone disease to the EuroQoL EQ-5D-5L.

This allows for health utilities to be estimated for cost-effectiveness analyses, based on responses to the ALSFRS-R.

3. What insights does the paper provide for informing health care-related decision making?

The ALSFRS-R can be used to estimate EQ-5D-5L utilities when they have not been collected directly within a trial.

Abstract

Background: The Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R) is the preferred measure of health outcome in clinical trials in motor neurone disease (MND). However it does not provide a preference-based health utility score, required for estimating QALYs in economic evaluations for health technology assessments.

Methods: Direct mapping models were developed using Ordinary Least Squares (OLS) and Tobit regression analyses to estimate EQ-5D-5L utilities (based on English tariffs) with ALSFRS-R total, domain and item scores used as explanatory variables, using patient-level data from a UK cohort study. Indirect mapping models were also used to map EQ-5D-5L domains, using the same variables, along with the Neuropathic Pain Scale (NPS) and Hospital and Anxiety Depression Scale for MND (MND-HADS) using multinomial logistic regression analysis. Goodness-of-fit was assessed along with predicted values for each mapping model.

Results: The best performing model predicting EQ-5D-5L utilities used 5 items of the ALSFRS-R items as explanatory variables in a stepwise OLS regression. The mean squared error was 0.0228, and the absolute mean error was 0.1173. Prediction was good, with 55.4% of estimated values within 0.1 and 91.4% within 0.25 of the observed EQ-5D-5L utility value. Indirect mapping using the NPS and HADS provided less predictive power than direct mapping models.

Conclusion: This is the first study to present mapping algorithms to 'crosswalk' between ALSFRS-R and EQ-5D-5L. This analysis demonstrates that the ALSFRS-R can be used to estimate EQ-5D-5L utilities when they have not been collected directly within a trial.

1. Introduction

Motor Neurone Disease (MND) (also known as Amyotrophic Lateral Sclerosis, ALS) is a progressively degenerative neurological condition, which affects the motor neurones in the brain and spinal cord. Life expectancy is between 3 to 5 years from symptom onset [1] and quality of life (QoL) is greatly impaired. Established treatments are symptom management, riluzole which increases median survival by about 3 months [2], and palliative care [3].

The recent approval of edaravone [4] by the US Food and Drug Administration (FDA) and the development of other new treatments options [5,6] will increase the need for evidence to support health technology assessment (HTA) and reimbursement decisions. At present, there is limited literature on preference-based health utilities in patients with MND [7], which are required for the calculation of quality-adjusted life-years (QALYs) for cost-utility analyses.

The EuroQoL EQ-5D is the preferred measure of the National Institute for Health and Care Excellence (NICE) [8] for calculating QALYs and the most widely used generic preference-based health outcomes measure, facilitating comparisons of health technologies between different diseases [9]. However, concerns have been expressed in applying this measure to MND patients, as it does not account for a range of symptoms, including communication, fatigue, swallowing and respiratory difficulty [1]. Previous experience of the EQ-5D-3L version in patients with MND, is that the measure can be used but with cautions of ceiling/floor effects, amongst other issues [10,11].

When EQ-5D data are not available, NICE allows for utilities be estimated by mapping from other health-related QoL measures [12]. A number of studies concerned with mapping disease-specific QoL instruments to the EQ-5D have been published [8,13] and guidelines produced for best practice [14,15]. Mapping from a non-preference based measure to the EQ-5D can be performed by predicting either the EQ-5D health utility values (direct mapping) or each of the five domain responses (indirect mapping). However, there is limited use of either approach in the context of neurological conditions [16,17].

The Amyotrophic Lateral Sclerosis Functioning Rating Scale-Revised (ALSFRS-R) [18] is recommended for use in clinical trials of treatments for MND [19] to capture clinical changes in areas of motor, bulbar and respiratory function. While this is not a preference-based measure, the ALS Utility Index, which is derived from 5 items of the ALSFRS-R and based on US general population tariff scores, does allow for utilities to be estimated [20], but has not been used in MND patients.

The aim of our study is to develop algorithms for mapping, both directly and indirectly, from measures used in MND clinical studies to allow for future prediction of EQ-5D-5L utility in populations of MND patients where utility data have not been collected.

2. Methods

2.1 Data

Data were sourced from the on-going Trajectories of Outcomes in Neurological Conditions (TONiC) study [21]. This longitudinal study of QoL and economic outcomes includes a large cohort of patients with MND recruited throughout the UK. Participants complete a series of outcome measures and provide demographic and clinical information.

For the analysis, we used baseline responses from a cross-section of patients recruited by MND clinical and research teams up to January 2017, who were at different stages of the disease course. Cross-sectional rather than longitudinal data were used as only 106 from 636 patients had returned any follow-up questionnaires at the time of analysis for this paper. All questionnaires used in the mapping analysis were returned in a single pack which the participant was requested to complete on the same day if possible. Clinicians allocated MND to limb, bulbar or respiratory onset types and performed disability assessment using the ALSFRS-R.

Ethical approval was granted from NRES Committee North West - Greater Manchester West (reference number 11/NW/0743).

2.2 Missing data

Mapping was only conducted for participants for whom complete data were available. A logistic regression was used to test whether participants who had returned incomplete questionnaires were comparable to those who had fully completed questionnaires, in terms of their age, gender, MND onset type, independent completion of questionnaires and recruiting centre.

2.3 Measures

The EQ-5D-5L was included in the TONiC study to estimate health utilities. It covers the health domains of mobility, self-care, usual activities, pain and anxiety/depression, each with five levels of severity [22]. A preference-based single index score can be generated with any combination of responses, anchored at 0 to represent death, 1 representing full health and, based on an English tariff, includes the worst health state of -0.281. These health utility values have been developed using general public responses to a standard gamble survey.

Three measures were selected from the TONiC dataset for the purposes of mapping to EQ-5D-5L:

1) ALSFRS-R, from which the ALS Utility Index was derived

The revised version of the ALSFRS incorporates respiratory items, increasing the sensitivity of the instrument to changes in the disease course of MND [18]. The ALSFRS-R is a validated MND-specific 12-item questionnaire, concerning bulbar, limb and respiratory function. Responses range from a score of 0 (severe problems) to 4 (no change). Responses to the ALSFRS-R are often used to derive a single index value and this value is reported in many clinical studies, but recent evidence suggests that the ALSFRS-R should be examined on a domain level, to generate either 3 or 4 domain scores to overcome concerns of unidimensionality [23] (Figure 1).

Insert Figure 1 here

The ALS Utility Index is derived from the following ALSFRS-R domains: speech and swallowing, eating and self-care, leg function and respiratory function [20]. Preference weights were generated

from members of the general public in the US using the standard gamble method and can be used to calculate a single preference-based utility score for persons with MND.

2) Neuropathic Pain Scale (NPS)

The Neuropathic Pain Scale [24] measures the intensity, unpleasantness and sharpness of neuropathic pain. The questionnaire consists of 10 scales with varying descriptions of pain, each with a possible response value between 0 (no pain) and 10 (worst pain imaginable). A further item concerns the length of time the patient has experienced pain with a score of between 0 and 2. Responses to the scales and the time item are summed to provide an NPS index score.

3) Hospital and Anxiety Depression Scale for MND (MND-HADS)

The MND-HADS [25] is a modified version of the Hospital and Anxiety Depression Scale (HADS) [26], developed for use in MND populations to address concerns that items in the original HADS may be confounded by physical disability. The modified HADS-A and HADS-D, which have acceptable psychometric properties, resulted from the removal of one item from both 7-item scales.

2.4 Statistical methods

With our aim of developing a crosswalk between the selected measures available in the TONiC study and the EuroQoL EQ-5D-5L, we tested a variety of model types and structures to arrive at a preferred model, and present alternative acceptable models that may suit different scenarios depending on data availability. Models based on direct mapping to EQ-5D-5L utilities (based on the English tariff [22]) and indirect mapping to EQ-5D-5L domains were tested. We randomly divided our dataset into estimation and validation samples in a 2:1 ratio, allowing algorithms generated in the estimation sample to predict values in the validation sample.

For the direct mapping analysis, we considered the ALSFRS-R by individual items, 3 and 4 domains variables and index score (Table 1; Figure 1). Individual item responses to the ALSFRS-R provide the greatest granularity; domain variables of the ALSFRS-R offer more concise information

on distinctive features of MND [23], and the index score was selected based on it being reported in many clinical studies in MND. The ALSUI was analysed by index score only as this measure is preference-based and therefore the index value combined weighted domain responses.

Two model types were chosen for the direct mapping. Firstly, we used ordinary least squares (OLS) regression which has been used extensively in comparable studies with acceptable performance [13]. Given that EQ-5D-5L utility data are skewed, however, violating the assumption of normality, and are censored at the upper limit of 1, we also used a Tobit regression model [27], and compared the results with OLS regressions models.

For all indirect mapping analyses, we used multinomial logistic regression to account for the categorical nature of EQ-5D domains, and the ordering of EQ-5D domain levels (Table 1). Initially, we used the same combinations of explanatory variables as in our direct mapping analysis. We then undertook a second indirect mapping analysis, which included the additional measures of the NPS and MND-HADS. These were included to overcome the lack of pain and mental health domains within the ALSFRS-R, therefore aiding our indirect mapping analysis. All models, direct and indirect, were run with and without the demographic variables of age, gender and MND onset type. All regression analyses were performed on the estimation sample, with generated results used to predict values using the validation sample. Furthermore a stepwise selection was used to examine if a reduced ALSFRS-R item model was more appropriate, in regards to removing variables whose coefficients were not rationally directed, and to test if a more efficient model could be obtained.

Data management was carried out using Microsoft Excel (Microsoft, Washington, USA) and R statistical software version 3.0 (Vienna, Austria) [28] was used for statistical analysis.

2.5 Assessing Model Performance

Model performance was examined by the mean squared errors (MSE) and mean absolute errors (MAE), in line with mapping guidance [8,14], to identify the best predictive models. For optimal model selection, we used MSE results from our validation sample. The MAE was included to

complement the MSE analysis and ensure that models selected based on a lower MSE score also had a lower MAE score.

Tests of systematic bias in selected models, chosen by lowest MSE score, were performed by examining the percentage of predicted values which deviated from observed values by more than 0.10 and 0.25. In order to identify if the selected models performed better for particular ranges of utility values, we also present the errors for the following categories of EQ-5D-5L utility scores: <0, 0 to <0.2, 0.2 to <0.4, 0.4 to <0.6, 0.6 to <0.8, 0.8 to 1. The plotting of histograms of the residuals of observed and predicted values of the selected model provided visual evidence of the nature of errors present in the models. Examination of mean differences in utility values between data sets was also undertaken. Finally, the Akaike Information Criterion (AIC) [29] was used to test the fit of models with lowest MSE for each of the explanatory variable groups in the direct mapping and also for all indirect mapping models.

The conduct and reporting followed guidance from the MApping onto Preference-based measures reporting Standards (MAPS) statement [14].

3. Results

3.1 Data Characteristics

Questionnaires were posted to 958 patients. A response rate of 66.4% for our cross-sectional data set was achieved, resulting in 636 returned questionnaires. 41 were incomplete for direct mapping, leaving a total of 595 completed patient questionnaires for inclusion in this analysis. Respondents who did not fully complete questionnaires were not statistically different from those who returned completed questionnaires, with respect to the variables tested (supplementary appendix). For the direct mapping, 397 patients were randomly assigned to the estimation sample and 198 to the validation sample. For indirect mapping, 18 patients had not completed the required additional questionnaires, therefore 385 patients were in the estimation sample and 192 in the validation sample. Estimation and validation samples were well balanced in terms of age, gender split, MND

onset type (bulbar, limb and respiratory), severity of EQ-5D domain responses, their EQ-5D-5L and ALSUI utility values, and ALSFRS-R, NPS and MND-HADS scores (Tables 2 and 3). The mean age of respondents was 65.1 years, which is in line with reported average ages of MND patients, while the gender split of 61% male is also reflected within the literature [30].

Figure 2 shows the distributions of the EQ-5D-5L utilities, ALSFRS-R index values and ALSUI scores in both samples. The number of individuals reporting negative EQ-5D-5L in our full dataset was 13 (2.2%). EQ-5D-5L utility ranged from -0.21 to 1, whereas the ranges of other measures were: ALSFRS-R (1 to 48), ALSUI (0 to 1), NPS (0 to 85) and MND-HADS (0 to 28).

Insert Figure 2 here

The distributions of responses varied across the EQ-5D domains (Table 3), with mobility and usual activities associated with greater proportions of severe problems, compared to other domains, reflecting the impact of MND upon patients' motor functioning. There were fewer responses in the more severe categories of pain/discomfort, with 5 (0.8%), and anxiety/depression with 6 (1.0%) individuals reporting severe problems.

3.2 Model Performance

The results of our mapping analysis by model type are presented in Table 4. Patient demographics were significant predictors of EQ-5D-5L utilities in only model OLS 1b; results for the other models with demographic variables are therefore not presented.

Direct mapping

Direct mapping models were compared in terms of their fitted values deviating by more than 0.1 and 0.25 of the true utility. This ranged from 31.3% to 55.4% for within 0.10 of true value; and 56.3% and 91.4% within 0.25. Direct mapping models generally performed well in estimating mean utility in the estimation sample, with all models predicting the mean correctly to 2 decimal places. In the validation sample, however, only three mapping models predicted the mean to 2 decimal

places, and only three predicted negative utility values. Model OLS (5) demonstrated the lowest MSE (0.0245), MAE (0.1218) and AIC values in the validation sample; however it contained non-significant coefficients, and negative (counterintuitive) coefficients on items 1 to 4, and 12. For these reasons, among direct mapping models the use of the reduced ALSFRS-R item model with stepwise selection of explanatory variables (model OLS (6)) is preferred. While MSE (0.0228), MAE (0.1173) and AIC all indicated model OLS (6) to provide the best fit of the data, the predicted errors were not uniform across the range of EQ-5D-5L utility scores (Table 5). Larger errors were apparent for negative utilities and for utilities in the range of 0 to 0.2. Figure 3 presents the fitted versus observed values, and Figure 4 plots the residuals. The model was strongest when predicting values from 0.2 to 0.8. 91.7% of estimations were within 0.25 of the observed EQ-5D-5L values, with 55.4% within 0.10 of the true value. The algorithm generated from this regression is presented below:

EQ-5D-5L utility = 0.086203 + 0.057486*item6 + 0.046674*item7 + 0.058688*item8 + 0.035927*item9 + 0.021126*item10s

Insert Figures 3 and 4 here

Indirect mapping

All indirect mapping models using the ALSFRS-R or ALSUI were upwardly biased as they consistently predicted higher utility values. They reported higher MSEs and MAEs than the direct mapping models using the same clinical information, but while the use of the additional measures of the NPS and MND-HADS resulted in lower errors, these models did not outperform direct mapping models.

To researchers who may benefit from our mapping analysis, and recognising that data availability may differ from one study to another, we present the complete results of the best performing models for various levels of information required in the supplementary appendix.

4. Discussion

Our study provides evidence that the ALSFRS-R, conceptually, could be a good candidate for mapping to the EQ-5D-5L in MND patients as the domain themes which appear in the EQ-5D (pain and anxiety/depression) but not in the ALSFRS-R, are reported in less severe terms in MND patients. This may partially explain why our mapping results fell within the reported MSE ranges of other mapping studies [13],and allowed us to assert that mapping from the ALSFRS-R to the EQ-5D-5L is viable.

The various ALSFRS-R mapping models showed markedly better predictive results than the models using the ALSUI when estimating EQ-5D-5L utilities. This may be in part due to the use of US preference tariff in the ALSUI, contrasting with our use of the English EQ-5D-5L tariff given the population from which the data were derived; but also the different selection of ALSFRS-R domains in their construct. The ALSUI estimated utility from items 1, 6, 8, 10 and 12 of the ALSFRS-R, whereas our best fitting model, OLS (6) used items 6 to 10. More research is needed to confirm the external validity of the ALSUI, and the extent to which it can be used to complement generic preference-based measures. Based on our mapping analysis, we cannot recommend using this measure to crosswalk to the EQ-5D-5L in MND patients.

As with the majority of previous mapping studies, our analysis found OLS regressions to have the strongest predictive power, slightly bettering the results from the Tobit regressions for direct mapping [13]. Indirect mapping models with the same specifications as the direct models showed higher MSEs using a multinomial logistic regression and consistently estimated larger mean EQ-5D utilities compared to observed values. The addition of the NPS and HADS to the indirect models reduced reported MSEs, but not to the extent as estimated in the direct mapping models. Demographic information did not significantly improve predictive power of the models, with the exception of model 1b; this result has been reflected in other MND research [31].

Our preferred model OLS (6), using a selection of ALSFRS-R items as explanatory variables, had MSE and MAE values comparable to other neurological statistical mapping work [16,17], and to errors reported in mapping studies in general [13]. The fact that our most accurate model, in terms of lowest MSE, contained only 5 items from the 12 item ALSFRS-R highlights the limitations of the use of the EQ-5D-5L within MND populations. There are characteristics of the disease, as defined by the main disease-specific measure in MND, that do not influence the metric of EQ-5D-5L health utility. These are: communication, salivation, swallowing, hand use, and respiratory function.

This study is a useful addition to the literature, in that it presents results for both direct and indirect mapping algorithms, using a variety of model structures. Few previous mapping studies have carried out both approaches on the same dataset [13]. Ours is the first study, to our knowledge, to have carried out such an analysis within an MND population, and provides useful evidence for the development of economic analyses in MND where EQ-5D data have not been collected directly. A strength of the analysis was the completeness of returned questionnaires with no evidence that data were not missing at random.

Our analysis may have been more robust, however, if we had access to data for a greater number of patients. In being a longitudinal study, TONiC offered the opportunity for an analysis of repeated measures to increase the power of the study, but as only 106 (of 636 patients) had returned at least 1 follow-up questionnaire pack at our cut-off date, we considered this to be an insufficiently representative sample for such an analysis. TONiC nonetheless represents both the largest and one of the most detailed quality of life studies for MND in the world. The strongest models within this study were unable to predict negative utility values for patients with MND, and had a higher error rate for low utility scores. This is of concern as MND is associated with relatively low utility values reflecting very poor health-related quality of life, although our data had only a few patients reporting negative utilities (2.2%). The mapping algorithms presented in this study were validated

from a sample of data which stems from the same study. While this is commonplace in the literature [13-15], external validation would have been preferable in the context of assessing broader generalisability. Finally, it should be noted that directly collected data on EQ-5D-5L utilities always supersedes predicted values based on mapping algorithms.

5. Conclusion

Many studies in MND have not used preference-based utility measures, which are required increasingly to support health technology assessment and reimbursement decisions. The algorithms presented here provide an option for estimating EQ-5D-5L utility when this has not been collected directly from MND patients. This study has shown that it is possible to predict, with reasonable accuracy (based on reported MSE ranges for other mapping studies), EQ-5D-5L utility values from the ALSFRS-R. It is also possible to map indirectly to EQ-5D-5L domains if the NPS and MND-HADS have been used alongside the ALSFRS-R. These findings should aid health technology assessment of interventions for MND, by providing evidence linking commonly used clinical outcome measures to a widely adopted generic preference-based measure, the EQ-5D-5L.

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Table 1: Mapping models used in statistical analysis

Model number	Explanatory variables	Statistical methods
Direct Mapping		
1a	ALSFRS-R Index	OLS and Tobit
1b	ALSFRS-R Index and demographics	OLS and Tobit
2	ALSFRS-R 4 Domains	OLS and Tobit
3	ALSFRS-R 3 Domains	OLS and Tobit
4	ALS Utility Index	OLS and Tobit
5	ALSFRS-R items	OLS and Tobit
6	Stepwise ALSFRS-R items	OLS and Tobit
Indirect mapping		
7	ALSFRS-R Index	Multinomial Logistic
8	ALSFRS-R 4 Domains	Multinomial Logistic
9	ALSFRS-R 3 Domains	Multinomial Logistic
10	ALS Utility Index	Multinomial Logistic
11	ALSFRS-R items	Multinomial Logistic
12	Stepwise ALSFRS-R items	Multinomial Logistic
13	ALSFRS-R index score, NPS and MND-HADS	Multinomial Logistic
14	ALSFRS-R 4 domains, NPS and MND-HADS	Multinomial Logistic
15	ALSFRS-R 3 domains, NPS and MND-HADS	Multinomial Logistic
16	ALSUI score, NPS and MND-HADS	Multinomial Logistic
17	ALSFRS-R items, NPS and MND-HADS	Multinomial Logistic
18	ALSFRS-R Items stepwise selection, NPS and MND-HADS	Multinomial Logistic

Table 2 – Patient characteristics

Characteristic	**Whole sample** (n=595)	**Estimation sample** (n=397)	**Validation sample** (n=198)
Demographics			
Male n (%)	363 (61.0)	243 (61.2)	120 (60.6)
Age mean (SD)	65.07 (10.89)	65.25 (10.89)	64.70 (10.6)
MND Onset n (%)			
Limb	404 (69.9)	265 (66.8)	139 (70.2)
Bulbar n (%)	159 (26.7)	112 (28.2)	48 (26.7)
Respiratory n (%)	11 (2.5)	8 (2.0)	3 (2.5)
Measures mean (SD)			
EQ-5D-5L index	0.57 (0.26)	0.57 (0.26)	0.58 (0.27)
EQ-5D VAS	0.60 (21.30)	0.61 (22.01)	0.60 (21.78)
ALSFRS-R score	31.95 (8.33)	31.85 (8.13)	32.15 (8.73)
ALS Utility Index	0.40 (0.24)	0.40 (0.24)	0.41 (0.24)
Neuropathic Pain Scale	30.02 (16.40)	28.74 (16.95)	32.62 (15.01)
MND-HADS	8.02 (5.45)	7.90 (5.51)	8.25 (5.32)

Table 3 – Distribution of responses by EQ-5D-5L domains

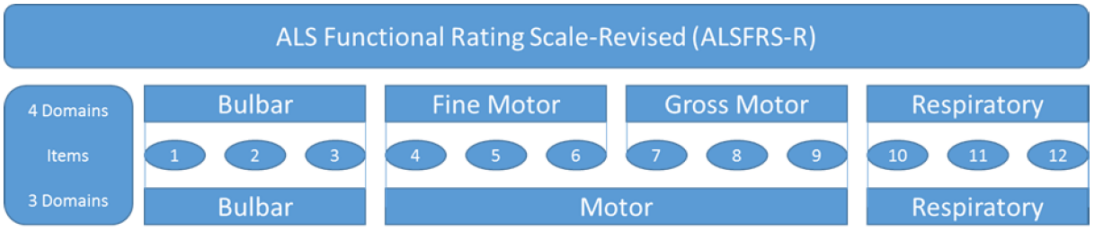
EQ-5D Domain	**Whole Sample** (n=595)	**Estimation Sample** (n=397)	**Validation Sample** (n=198)
Mobility	n (%)	n (%)	n (%)
Level 1	99 (16.6)	63 (15.9)	36 (18.2)
Level 2	81 (13.2)	54 (13.6)	27 (17.6)
Level 3	157 (26.4)	106 (26.4)	52 (26.3)
Level 4	152 (25.6)	100 (25.2)	52 (26.3)
Level 5	106 (17.8)	75 (18.9)	31 (15.7)
Self-care			
Level 1	118 (19.8)	85 (21.4)	33 (16.7)
Level 2	152 (25.6)	88 (22.2)	64 (32.3)
Level 3	162 (27.2)	110 (27.7)	52 (26.3)
Level 4	71 (11.9)	52 (13.1)	19 (9.6)
Level 5	92 (15.5)	62 (15.6)	30 (15.2)
Usual Activities			
Level 1	53 (8.9)	35 (8.8)	18 (9.1)
Level 2	117 (19.7)	71 (17.9)	46 (23.2)
Level 3	174 (29.2)	118 (29.7)	56 (28.3)
Level 4	118 (19.8)	85 (21.4)	33 (16.7)
Level 5	115 (22.4)	88 (22.2)	45 (27.7)
Pain/discomfort			
Level 1	179 (30.1)	116 (29.2)	63 (31.8)
Level 2	213 (33.8)	140 (35.3)	73 (36.9)
Level 3	161 (27.1)	114 (28.7)	47 (23.7)
Level 4	37 (3.6)	22 (5.5)	15 (7.6)
Level 5	5 (0.8)	5 (1.3)	0 (0.0)
Anxiety/depression			
Level 1	268 (45.1)	181 (45.6)	87 (43.9)
Level 2	203 (34.1)	131 (33.0)	72 (36.4)
Level 3	98 (16.5)	66 (16.6)	32 (16.2)
Level 4	20 (3.3)	15 (3.8)	5 (2.3)
Level 5	6 (1.0)	4 (1.0)	2 (1.0)

Table 4 – Mapping results

Model	**Estimation Sample (n=397)**				**Validation Sample (n=198)**			
	Mean (SD)	Min, Max	MSE	MAE	Mean (SD)	Min, Max	MSE	MAE
Observed EQ-5D-5L utility	0.57 (0.26)	-0.2, 1	N/A	N/A	0.58 (0.26)	-0.21, 1	N/A	N/A
Direct Models								
OLS (1)	0.57 (0.19)	0.1, 0.86	0.0404	0.1594	0.57 (0.18)	-0.06, 0.9	0.037	0.1552
OLS (1b)	0.57 (0.19)	0.04, 1	0.0339	0.1448	0.57 (0.19)	-0.06, 1	0.0306	0.1407
OLS (2)	0.57 (0.21)	0.08, 0.96	0.0239	0.1202	0.57 (0.15)	0.1, 0.96	0.0461	0.1794
OLS (3)	0.57 (0.20)	0.05, 0.94	0.0447	0.1245	0.57 (0.15)	0.08, 0.94	0.0281	0.1306
OLS (4)	0.57 (0.16)	0.03, 0.92	0.0219	0.1201	0.57 (0.16)	0.3, 0.95	0.0441	0.1731
OLS (5)	0.57 (0.22)	0.09, 0.98	0.0224	0.1135	0.57 (0.22)	0.1, 0.98	0.0245	0.1218
OLS (6)	0.57 (0.21)	0.09, 0.96	0.0221	0.1112	0.58 (0.21)	0.1, 0.97	0.0228	0.1173
Tobit (1)	0.57 (0.17)	0.09, 0.87	0.0405	0.1589	0.59 (0.18)	-0.06, 0.91	0.0371	0.1545
Tobit (1b)	0.57 (0.19)	0.05,0.99	0.0356	0.1453	0.57 (0.20)	-0.01,0.92	0.0310	0.1423
Tobit (2)	0.57 (0.17)	0.07, 0.85	0.0421	0.1625	0.51 (0.15)	0.03, 0.81	0.0466	0.1801
Tobit (3)	0.57 (0.21)	0.03, 0.97	0.0271	0.1283	0.55 (0.20)	0.01, 0.92	0.0280	0.1329
Tobit (4)	0.57 (0.16)	0.3, 0.93	0.0447	0.1711	0.58 (0.16)	0.3, 0.97	0.0442	0.1730
Tobit (5)	0.57 (0.22)	0.08, 1	0.0219	0.1132	0.57 (0.22)	0.09, 0.99	0.0255	0.1288
Tobit (6)	0.57 (0.21)	0.08, 0.9	0.0233	0.1149	0.57 (0.21)	0.09, 0.98	0.0250	0.1241
Indirect Models								
Mlogit (7)	0.65 (0.24)	0.17, 0.95	0.5660	0.1794	0.66 (0.23)	0.17, 1	0.0597	0.1812
Mlogit (8)	0.66 (0.22)	0.17, 1	0.0390	0.1285	0.67 (0.58)	0.17, 1	0.0320	0.1415
Mlogit (9)	0.64 (0.24)	0.17, 1	0.0360	0.1379	0.60 (0.25)	-0.02, 1	0.0303	0.1342
Mlogit (10)	0.61 (0.23)	0.17, 1	0.0501	0.1811	0.62 (0.22)	0.17, 0.95	0.0510	0.1732
Mlogit (11)	0.62 (0.21)	0.01, 0.95	0.0274	0.1165	0.62 (0.22)	-0.02, 1	0.0315	0.1526
Mlogit (12)	0.61 (0.22)	0.01, 0.95	0.0252	0.1140	0.62 (0.21)	-0.02, 1	0.0310	0.1563

Mlogit (13)	0.57 (0.22)	-0.07, 1	0.0199	0.1034	0.58 (0.22)	-0.02, 1	0.0308	0.1310
Mlogit (14)	0.72 (0.23)	0.34,1	0.0989	0.2421	0.58 (0.21)	0.17,1	0.0534	0.2181
Mlogit (14)	0.74 (0.22)	0.49, 0.93	0.0954	0.2339	0.60 (0.21)	0.34, 0.94	0.0663	0.2316
Mlogit (15)	0.59 (0.23)	0.09, 1	0.1581	0.1581	0.59 (0.22)	-0.02, 1	0.0497	0.1757
Mlogit (16)	0.49 (0.22)	-0.09, 1	0.1870	0.1870	0.51 (0.11)	0.51, 1	0.0657	0.1956
Mlogit (17)	0.59 (0.22)	-0.1, 1	0.2010	0.2010	0.59 (0.21)	0.17, 1	0.0441	0.2301

Figure 1 – Structure of ALSFRS-R, showing breakdown by 4 and 3 domains and items



Bulbar items are related to speech and communication. The fine motor domain is concerned with actions such as hand and finger movements, whereas gross motor captures changes in areas such as walking and climbing. The respiratory domain captures issues around the ease of breathing.

Figure 2: Distributions of EQ-5D-5L utilities, ALSFRS-R Index scores and ALSUI scores by sample

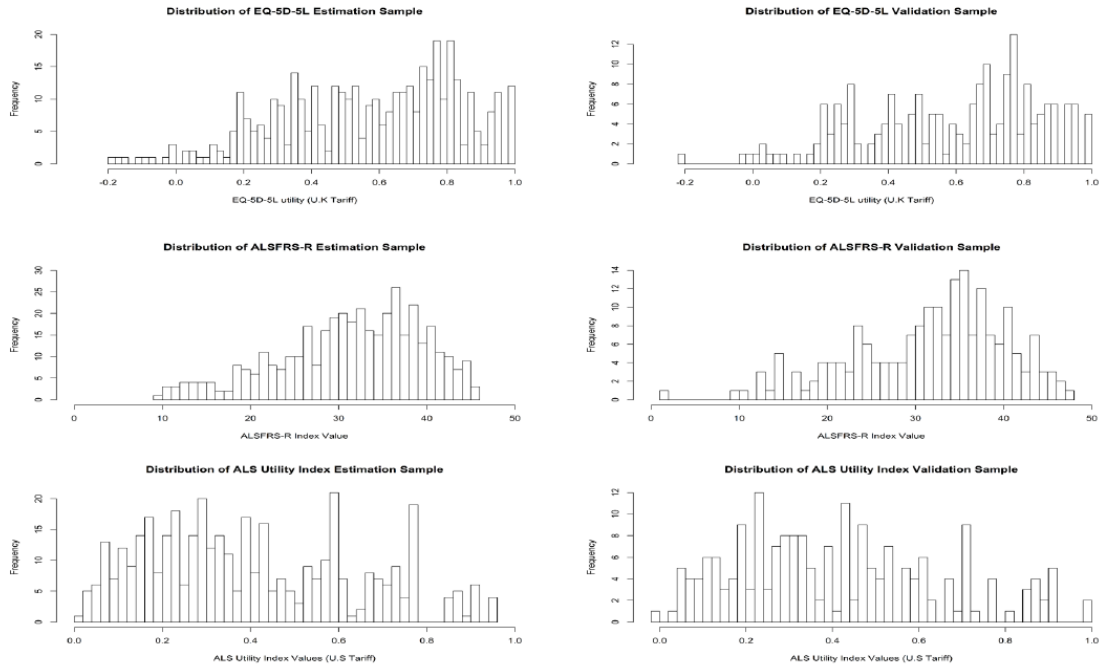


Figure 3 – Selected model OLS (6) fitted values v observed values, validation sample

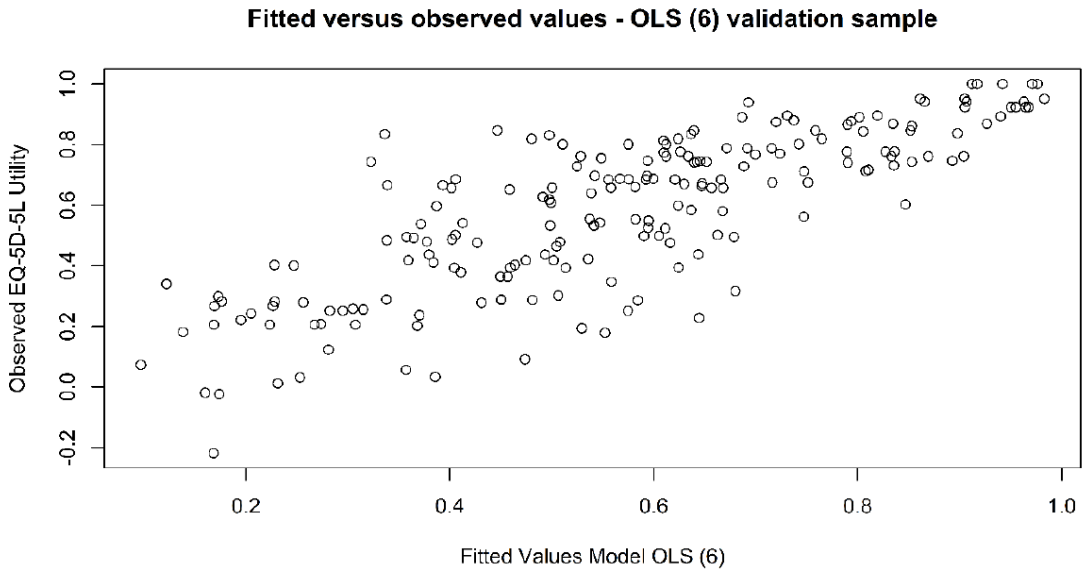


Figure 4 – Residuals of selected model OLS (6), based on the validation sample